DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC - 9 1998

TRANSMITTED VIA FACSIMILE

Robert W. Ashworth, Ph.D.
Director, Regulatory Affairs
Knoll Pharmaceutical Company
199 Cherry Hill Road
Parsippany, NJ 07054

Re: **NDA 20-716**
Vicoprofen (hydrocodone bitratrate 7.5 mg. and ibuprofen 200 mg)
MACMIS ID# 6100

Dear Dr. Ashworth:

The Division of Drug Marketing, Advertising, and Communications (DDMAC), as part of its routine monitoring and surveillance program, has reviewed materials used by Knoll Laboratories to promote its product, Vicoprofen.[1] DDMAC has determined that these materials and other materials containing similar claims are false and misleading in violation of the Federal Food, Drug, and Cosmetic Act and applicable regulations.

Limitations in Indication

The Indications and Usage section of the package insert for Vicoprofen contains two important limitations, namely that "Vicoprofen is indicated for the **"short term (generally less than 10 days)** management of acute pain" and "Vicoprofen is **not indicated** for the treatment of such conditions as osteoarthritis or rheumatoid arthritis [emphasis added]." These two important limitations on use are omitted from Vicoprofen's promotional pieces, leaving the impression that this drug may be used safely and effectively in the management of long-term pain, and for any conditions involving pain, including conditions such as osteoarthritis and rheumatoid arthritis.

1 These materials include Journal Ad VCP-0697-094/9-97, Journal Ad VCP-0798-212, Health Care Provider Letter VCP-0897-179/8-97, and Sales Aid VCP-0598-173/7-98.

A. Short-term Use Limitation

Knoll implies that Vicoprofen is indicated for long-term use by suggesting that easy and multiple refills are available. Statements such as "up to five refills within a 6 month period suggest usage beyond the short-term use indicated. The prescription pad graphic and accompanying claims suggest several months' use.

B. Lack of Indication for Treatment of Arthritis Pain

The multiple graphics of bones and joints suggests a variety of pain conditions that do not exclude the treatment of osteoarthritis and rheumatoid arthritis. The absence of a clear and prominent disclosure that Vicoprofen is not approved for the relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis is especially misleading within this graphical context. For example, Summary Sales Aid VCP-0598-173/07/98 shows graphics of the spinal column, entitled "back disorders" which includes the treatment of osteoarthritis or rheumatoid arthritis. In addition, the accompanying header alludes to the "broad range" of clinical applications. Both the content and the context of this message are misleading because it implies that Vicoprofen may be used for an unapproved use and for an unapproved length of time.

Rapid Onset of Action Claim

A. Estimation of Rapid Onset Prior to First Measurement of Pain Relief

Brochure VCP-0598-173 claims a rapid onset of action, ranging from 11.0 to 16.2 minutes in clinical trials. Two charts are included in the brochure, one of which depicts onset of action and the other depicts drug efficacy. The onset of action chart is actually a portion of the efficacy chart. DDMAC requested and Knoll submitted the data on file referenced to substantiate the rapid onset of action claim. These data are based on self-reported patient pain measurements that first began to be measured at 0.3 hours (18 minutes). A backward linear interpolation of this data was later performed by Knoll, to provide an "estimated" rapid onset of action for Vicoprofen of a 13.1 minutes, based on an *estimated* range of onset of 11.0 to 16.2 minutes. There is no evidence to support the assumption that a linear progression of pain relief occurred within this initial time range or that any onset of action occurred prior to measurement of the first time point in the study, i.e. 18 minutes. Thus, the claim of a rapid range of onset of action is not substantiated by adequate data, and thus, is false and misleading and misbrands Vicoprofen.

B. Exclusion of the Placebo Arm in Graphed Data

Neither the efficacy graph nor the onset of action graph for Vicoprofen includes the plot of the placebo arm of the study. The data on file, which Knoll has submitted, to DDMAC shows that Vicoprofen's *estimated* time to pain-relief is 13.1 minutes, with a

range of 11.0 to 16.2 minutes, whereas the placebo's *estimated* time to pain relief was 15.5 minutes with a range of 12.6 minutes to 20.4 minutes. A difference of onset of 1 or 2 minutes in self-reported patient pain relief between Vicoprofen and a placebo, would not appear to be of clinical significance and would not provide substantial evidence to support the claim of rapid onset of action. The omission of the placebo arm from both graphs is inherently misleading.

Fair Balance

Knoll's promotional materials have increasingly obscured the prominence and readability of important safety information by using busy backgrounds to "bleed" the risk information text into the picture behind it. One example of such a background is seen in Journal Ad VCP-0798-212/8-98, where a orange and black spotted leopard provides the background for white printed safety information. Another example is seen in Journal Ad VCP-0798-210/8-98, where the background of soft pastel sand decreases the contrast of the white-printed safety information. The efficacy information in this same ad, however, is presented with stark clarity in red and black print located within a (red-bordered) white message box strategically located so as to stand out beside the busy graphic background. Both of these pieces, and others like them, fail to present information relating to side effects and contraindications with a prominence and readability reasonably comparable with the presentation of information relating to effectiveness of the drug, taking into account all implementing factors such as typography, layout, contrast, headlines, paragraphing, white space, and any other techniques apt to achieve emphasis. See 21 C.F.R. §202.1(e)(7)(viii).

In order to address these violations, DDMAC requests that Knoll take the following actions:

1. Immediately discontinue the dissemination and use of the violative pieces noted in this letter and any other promotional materials that contain similar claims.

2. Provide a written response to DDMAC of your intent to comply with the above request, and a list of promotional materials containing the misleading presentations that will be discontinued.

Knoll's response should be received by December 19, 1998. If Knoll has any further questions or comments, please contact the undersigned or Norman Drezin, Esq., by facsimile at (301) 594-6759, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-40, Rm. 17B-04, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds you that only written communications are

communications are considered official.

In all future correspondence regarding this action, please refer to MACMIS ID #6100 in addition to the drug NDA number.

Sincerely,

Patricia Kuker Staub, Esq. R.Ph.
Regulatory Counsel
Division of Drug Marketing,
Advertising, and Communications